Response of Extraabdominal Desmoid Tumors to Therapy with Imatinib Mesylate

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BACKGROUND. Desmoid tumor represents a rare monoclonal neoplasm arising from deep musculoaponeurotic structures and may occur sporadically or in association with the familial adenomatous polyposis and Gardner syndromes. Desmoid tumors do not appear to demonstrate metastatic potential; however, local infiltrative growth results in significant morbidity and potential mortality. Although the delineation of optimal therapy for desmoid tumors has been confounded by several factors, surgical resection with adjuvant radiotherapy for a positive surgical margin remains the standard approach. Responses have been demonstrated to nonsteroidal antiinflammatory agents, antiestrogen compounds, and a variety of other agents in small series. Imatinib mesylate appears to demonstrate inhibitory activity against multiple class 3 receptor tyrosine kinases, including platelet-derived growth factor receptor (PDGFR)-α and PDGFR-β, as well as c-*kit*.

METHODS. The authors performed immunohistochemical and qualitative real-time polymerase chain reaction analysis on nine desmoid tumor specimens that demonstrated consistent positivity for c-*kit* as well as PDGFR-α and PDGFR-β. At the time of last follow-up, 2 patients had received therapy with imatinib mesylate at a dose of 400 mg twice daily.

RESULTS. Both patients demonstrated ongoing radiographic and clinical responses with a duration of 9 months and 11 months, respectively.

CONCLUSIONS. Imatinib mesylate has been reported to have activity against desmoid tumor, most likely because of c-*kit* and PDGFR receptor tyrosine kinase activity inhibition, and warrants further study. The relative novelty of this agent and the lack of long-term toxicity data should prompt its use only in the salvage setting in which established local and systemic approaches fail to control disease. In addition, the use of imatinib mesylate in the treatment of this neoplasm preferably should be in the context of a formal prospective clinical trial. ***Cancer* 2002;95:2373–9.** © *2002 American Cancer Society.*
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Desmoid tumor, also known as aggressive fibromatosis, represents a rare monoclonal neoplasm arising from deep musculoaponeurotic structures.[1–3] Reported to affect approximately 2–4 per million persons annually, desmoid tumor may occur sporadically or in association with the familial adenomatous polyposis (FAP) syndrome and Gardner syndrome.[4–6] Women of childbearing age are reported to be affected most often.[7]

To our knowledge the specific etiologic mechanisms that give rise to this neoplasm are poorly understood. The observation of clonal cytogenetics in both FAP-associated and sporadic desmoid tumor

supports a genetic predisposition for the development of this disease.[2–4] Prior trauma or surgery,[8–13] as well as endogenous or exogenous estrogen exposure, also appear to play a contributory role.[7,8,14,15] Although the overwhelming majority of FAP-associated diagnoses occur in the abdomen or abdominal wall, approximately only 50% of the reported sporadic cases occur in this anatomic location. The soft tissues of the shoulder, neck, and chest wall constitute the majority of the remaining sites of occurrence, with the extremities being involved in a minority of patients.[14] Although desmoid tumors do not demonstrate metastatic potential, the morbidity that results from this disease and its treatment cannot be understated. Local infiltrative growth and tissue invasion can result in pain, deformity, functional impairment, and death when vital organs are involved.[14,16,17] The attendant morbidity and mortality from these tumors is highly site-dependent. Intraabdominal desmoid infiltration of vital organs reportedly leads to a 10-year mortality rate of approximately 37%.[14] Mortality is rare among patients with extraabdominal desmoid tumors; however, the disfigurement and loss of function that result from tumor progression or its treatment is significant.

The delineation of optimal therapy for desmoid tumor has been confounded by the rarity of the diagnosis, as well as a lack of randomized and prospective direct comparisons of treatment approaches. Also problematic is the inclusion in a majority of studies of varied anatomic presentations, thereby limiting the ability to draw definitive conclusions regarding efficacy. Generally accepted rates of local recurrence after surgical excision are approximately 30–50%.[16–24] This reflects the impact of tumor location and the ability of the surgeon to achieve negative surgical margins. At doses of 50–60 Gy, definitive radiotherapy has demonstrated local control rates of 75% in cases in which surgery is not feasible.[19] Adjuvant radiotherapy has been shown to reduce recurrence rates by as much as 50%, and may offset the negative prognostic impact of positive surgical margins, allowing for a surgical approach that balances local control with a significant impact on long-term function and morbidity.[16]

Despite having a relatively high local failure rate, surgical resection of extraabdominal desmoid tumors, with adjuvant radiotherapy for a positive surgical margin, remains the standard approach. Although primary radiotherapy can produce local control rates that are comparable to those achieved with surgery alone,[25] the risk of secondary malignancy and the potential for postradiation fibrosis make surgery the initial option of choice if a negative surgical margin resection is anticipated.

To our knowledge there are limited data with regard to outcome in patients with recurrent desmoid tumor. A minority of patients demonstrate durable benefit from surgical excision of recurrent disease.[11,24,26–28] However, a significant proportion of patients will experience local recurrences that are not amenable to surgical resection or radiotherapy. A variety of systemic therapy approaches therefore have become increasingly investigated and utilized. As is the case with local therapies, the data for systemic agents generally are limited to relatively small series reports. Variable anatomic locations and patient treatment history preclude comparisons between agents, and the durability of responses is to our knowledge underreported. It is important to note that there is likely significant reporting bias that may serve to exaggerate rates of success. Responses have been demonstrated using a variety of nonsteroidal antiinflammatory agents (NSAIDs), of which sulindac has a reported response rate of 50%.[29–32] This class of compounds inhibits cyclooxogenase activity, prevents activation of ornithine decarboxylase (ODC), and decreases intracellular levels of cyclic adenosine monophosphate (cAMP). Reported response rates to tamoxifen also approximate 50%. Antitumor activity likely results from the blockade of estrogen-dependent cellular proliferation, including the prevention of ODC activation.[10] Antagonistic effects on both platelet-derived growth factor-β (PDGF-β) production and prostaglandin metabolism also may contribute to the efficacy of this drug.[31,33–37] Conventional cytotoxic therapy also has demonstrated anecdotal success, occasionally producing prolonged progression-free periods.[11,26,35,38–44] In our experience, prolonged treatment confers a proportionally longer progression-free period; however, toxicity limits the duration and success of this approach.

A variety of other agents also have been employed in the treatment of desmoid tumor with variable success, including interferon,[45] ascorbic acid, theophylline, chlorthiazide, megestrol, and other progesterone formulations.[13–15,20,26,31]

Imatinib mesylate (Gleevec™; Novartis Pharmaceuticals, Hanover, NJ) represents a selective tyrosine kinase inhibitor. In addition to the antagonistic action against the dysregulated bcr-Abl fusion protein observed in patients with chronic myelogenous leukemia,[46,47] imatinib mesylate also possesses inhibitory activity against multiple class 3 receptor tyrosine kinases (RTKs), including PDGFR-α and PDGFR-β, as well as the c-*kit* subtype.[46] This agent blocks ligand-activated receptor phosphorylation and mitogen-activated kinase activation and proliferation, resulting in the inhibition of cellular growth and proliferation.[48] Inhibition of c-*kit* RTK activity is hypothesized to ac-

TABLE 1
Immunohistochemical/RT-PCR Characteristics of Nine Desmoid Tumors

Patient no.	Location	Status	c-Kit	PDGFR-α	PDGFR-β	PDGF-α	PDGF-β
1	Intraabdominal	Primary	−	+	+	NA	NA
2	Abdominal wall	Primary	+	+	+	NA	NA
3	Abdominal wall	Primary	+	+	+	NA	NA
4	Left arm	Primary	−	+	+	NA	NA
5	Abdominal wall	Primary	−	+	+	NA	NA
6	Right hip	Recurrent	+	+	+	NA	NA
7	Right thigh	Recurrent	+	+	+	+	+
8	Pelvic	Recurrent	+	+	+	+	+
9	Left chest wall	Recurrent	+	+	+	+	+

RT-PCR: reverse transcriptase-polymerase chain reaction; PDGFR: platelet-derived growth factor receptor; PDGF: platelet-derived growth factor; +: positive; NA: not available.

count for the dramatic responses observed in the majority of patients with gastrointestinal stromal tumors treated with imatinib mesylate).[49] Inhibition of PDGFR activity has produced dramatic cytoreduction in a murine dermatofibrosarcoma protuberans model,[50] and yielded clinical responses in this tumor subtype as well.[51]

After internal review board approval, we performed immunohistochemical (IHC) and qualitative real-time polymerase chain reaction analysis of nine desmoid tumor specimens. The results are summarized in Table 1, and selective IHC specimens are depicted in Figures 1–3. Figures 1–3 depict representative specimens, with IHC staining for PDGF-α, PDGF-β, and c-*kit*, respectively.

Two patients (Patients 7 and 9) received therapy with imatinab mesylate, and both demonstrated a response.

Case Reports

Patient 1 was diagnosed with a desmoid tumor involving the distal right lower extremity at the age of 15 years. There was no personal or family history of FAP, prior history of desmoid tumor, or features consistent with Gardner syndrome. Initial therapy was comprised of low-dose oral etoposide and methotrexate, despite which the patient experienced progressive disease. Partial amputation of the right forefoot and several digits was performed. Over the ensuing 4-year period, despite antiestrogen and nonsteroidal therapies, the patient required multiple resections of noncontiguous recurrent lesions involving the right calf and thigh. Two of these surgical procedures were followed by adjuvant radiotherapy for positive surgical margins. The patient experienced significant functional limitations of her right leg and gait as a result of her treatments. Eight months after her last resection, a 14 cm $\times$ 12 cm symptomatic desmoid tumor recurred at approximately the right sciatic nerve in the mid-

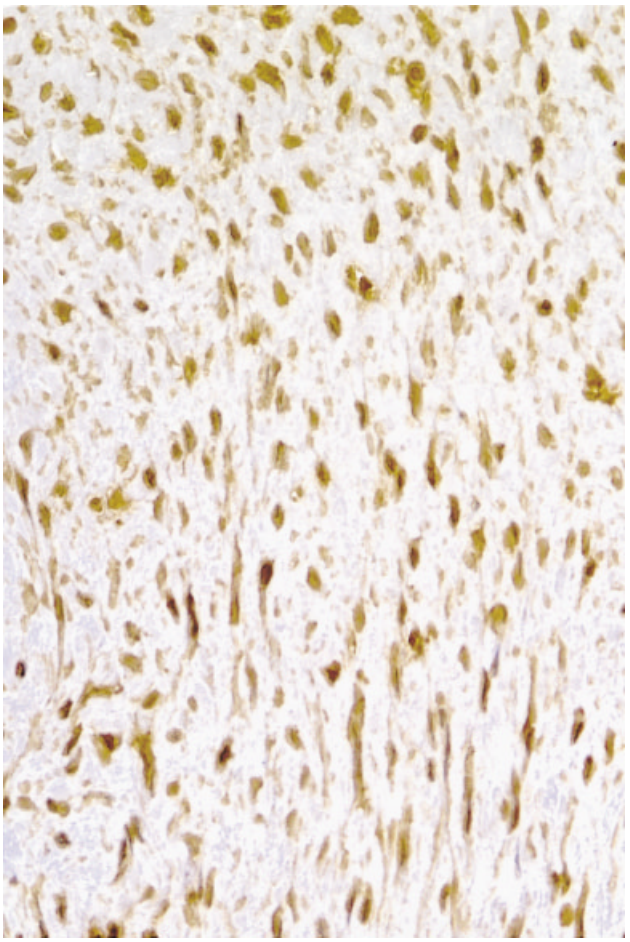

FIGURE 1. Immunohistochemical staining for platelet-derived growth factor receptor-α in a desmoid tumor specimen. Anti-PDGFR-α (Santa Cruz Biotech, Santa Cruz, CA; 1:200); avidin-biotin-peroxidase complex. Hematoxylin; original magnification $\times$ 400.

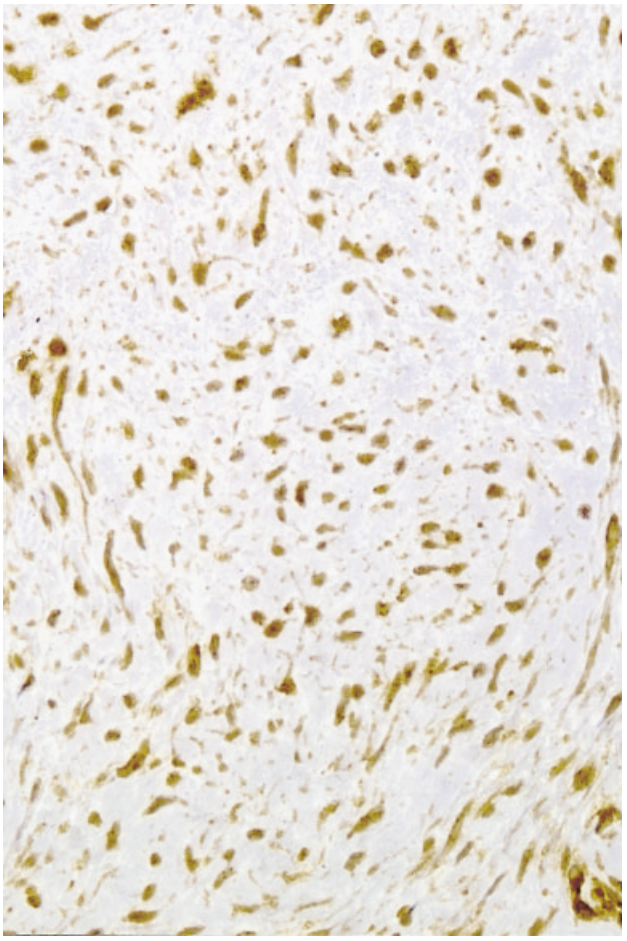

FIGURE 2. Immunohistochemical staining for platelet-derived growth factor receptor-β in a desmoid tumor specimen. Anti-PDGFR-β (Santa Cruz Biotech, 1:200); avidin-biotin-peroxidase complex. Hematoxylin; original magnification $\times$ 400.

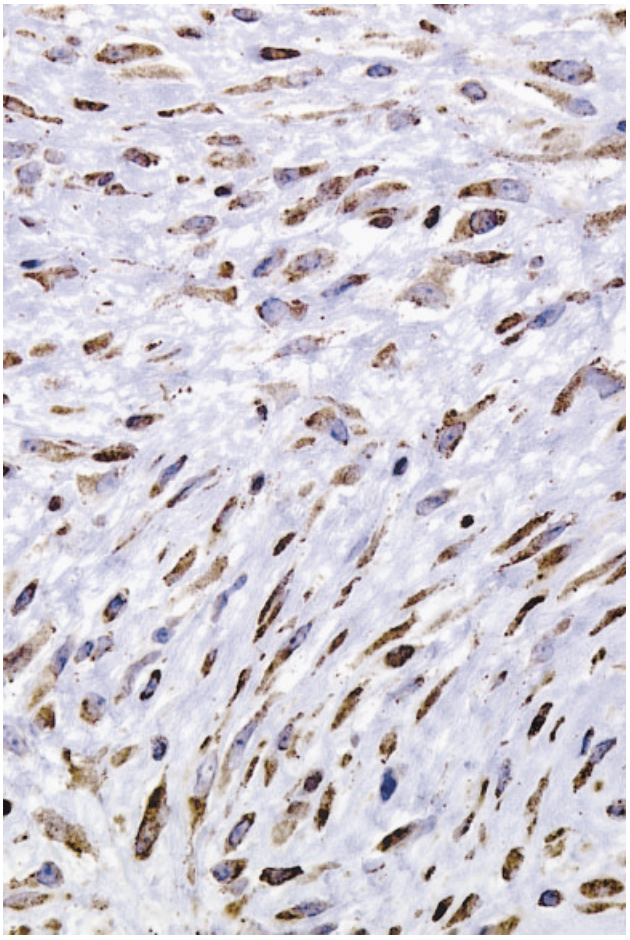

FIGURE 3. Immunohistochemical staining for c-*kit* in a desmoid tumor specimen. Anti c-*kit* (Dako Corp., Carpinteria, CA; 1:100); avidin-biotin-peroxidase complex. Hematoxylin; original magnification $\times$ 400.

thigh. A second lesion measuring 5 cm $\times$ 6 cm was noted in the soft tissues posterior to the right femoral neck, and was found to extend proximally into the distal right hemipelvis on magnetic resonance imaging. The patient sought consultation at the Sarcoma clinic at the University of Michigan Comprehensive Cancer Center in May 2001 after a hindquarter amputation was suggested. Concern regarding morbidity, as well as the ability of an amputation to control the entirety of her disease, resulted in the consideration of systemic therapy with imatinib mesylate. Therapy was initiated in June 2001. Figure 4 depicts the lesions prior to therapy. After 2 months of treatment at a dose of 400 mg twice daily (Fig. 5), significant improvement was noted. This trend continued over the next 6 months, with an overall approximate 50% reduction in the size of the tumor masses. At the time of last follow-up, the patient continued to demonstrate an ongoing response to therapy, with concomitant improvement in referable symptoms. Therapy has been well tolerated and has continued without any reported complications.

Patient 2 was a 39-year-old man who experienced extensive burns to his anterior trunk during childhood. He was diagnosed with a desmoid tumor involving the left pectoralis musculature in 1996, for which he underwent a radical mastectomy. Approximately 1 year later a symptomatic 12 cm $\times$ 8 cm local recurrence was noted on magnetic resonance imaging. Therapy with NSAIDs and tamoxifen proved ineffective, and low-dose oral etoposide and methotrexate was initiated. The patient demonstrated a partial response to chemotherapy that lasted for 34 months, after which worsening symptoms prompted the performance of magnetic resonance imaging. This revealed progression of the desmoid tumor of the left chest wall, and the patient was offered aggressive re-

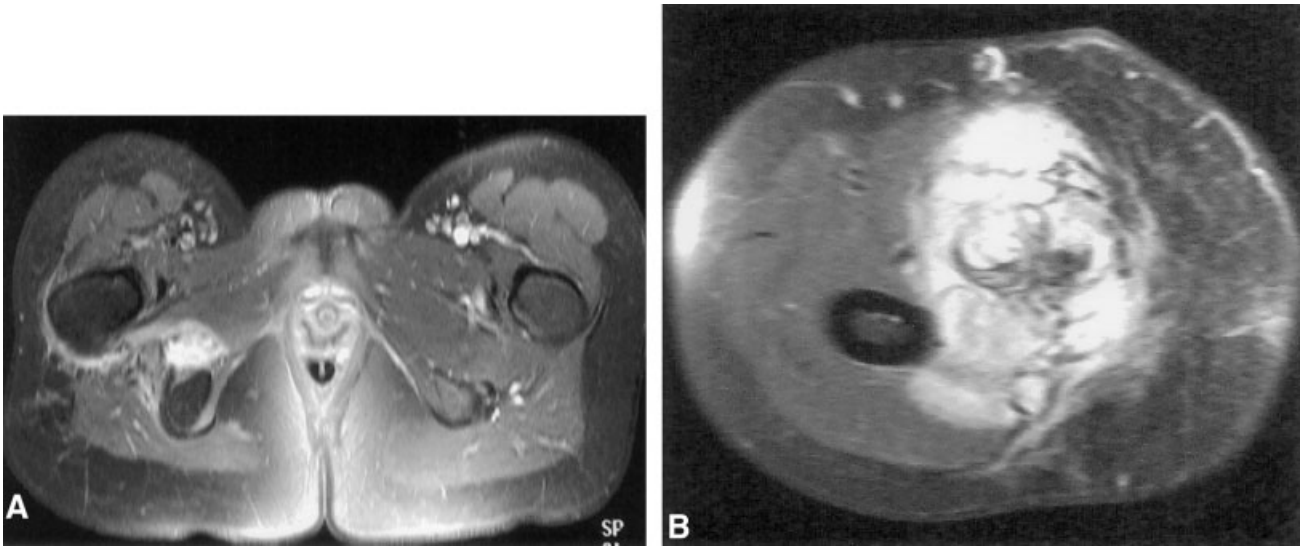

FIGURE 4. Desmoid lesions (A, B) in Patient 1 prior to therapy.

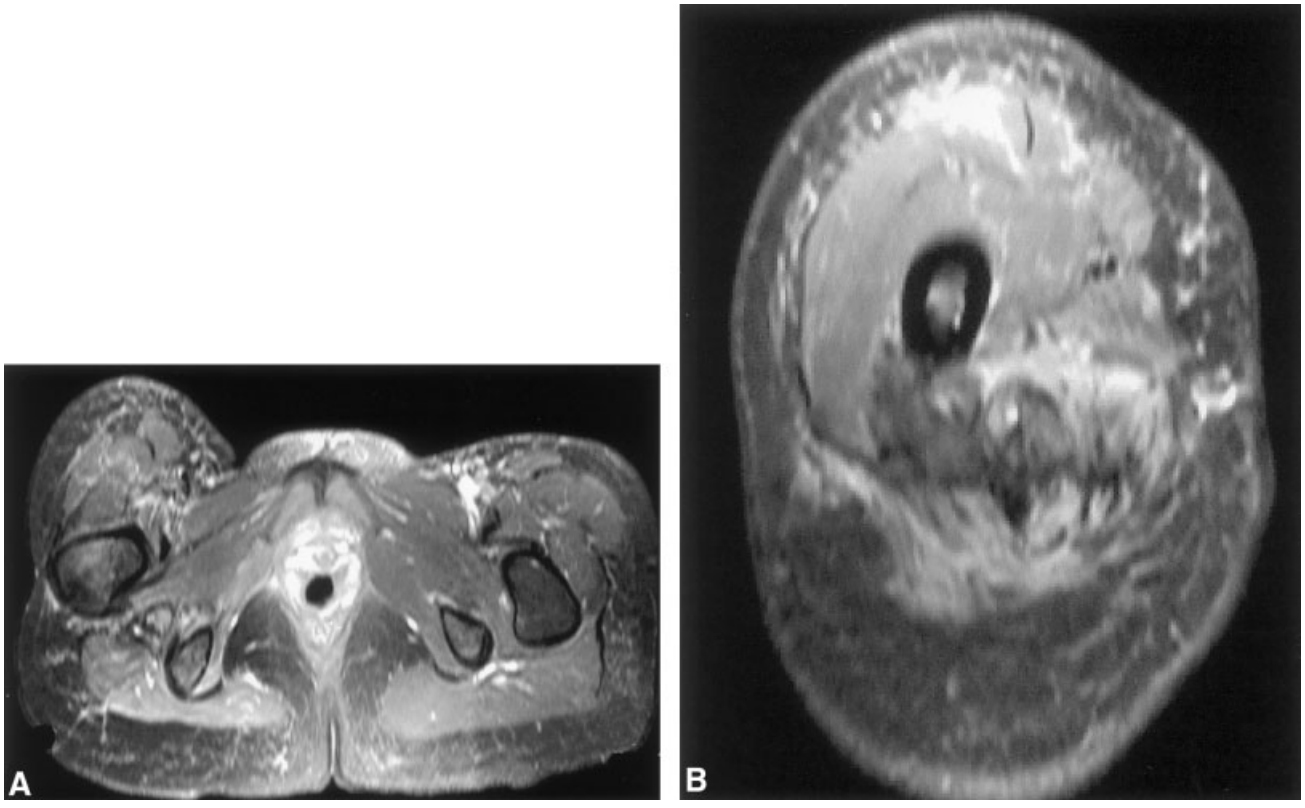

FIGURE 5. Desmoid lesions (A, B) in Patient 1 after 2 months of therapy.

section, which would likely entail a forequarter amputation. Once again, concern regarding the morbidity and efficacy of this approach was raised, and imatinib mesylate at a dose of 400 mg twice daily was initiated in August 2001. At the time of last follow-up, the patient's tumor was stable with respect to size; however, it demonstrated ongoing significant reductions in internal density and enhancement since therapy was initiated. The patient likewise was experiencing continued improvement of symptoms.

DISCUSSION

Desmoid tumor represents a therapeutic challenge that requires multidisciplinary collaboration from surgical, medical, and radiation oncologists. As a result of balancing local control with posttreatment function and morbidity, a significant number of patients will develop a disease recurrence despite surgery and radiotherapy. Although a reasonable proportion of patients will respond to "frontline" systemic therapies, including antiestrogen compounds and NSAIDs, many will develop progressive disease despite such treatments. Conventional chemotherapy, typically administered in low doses over a prolonged period of time, has demonstrated encouraging results; however, the duration of treatment inherently is limited by cumulative toxicity. Based on the IHC and reverse transcriptase-polymerase chain reaction characteristics of nine desmoid tumors, two young patients with heavily pretreated and recurrent desmoid tumors were treated with imatinib mesylate in an attempt to avoid the morbidity associated with amputation. Both patients were reported to have tolerated treatment, which at the time of last follow-up was ongoing at 9 months and 11 months, respectively. Both patients experienced radiographic responses with associated improvement in symptoms and function.

The use of imatinib mesylate in the treatment of desmoid tumors has produced encouraging preliminary results. However, the relative novelty of this agent and the lack of long-term toxicity data should prompt its use only in the salvage setting in which surgery, radiotherapy, and established systemic agents have failed to control disease. In addition, the use of imatinib mesylate in the treatment of this neoplasm preferably should be in the context of a formal prospective clinical trial. The North American Treatment Consortium of the Connective Tissue Oncology Society has initiated such a trial. Nonetheless, we conclude that imatinib mesylate has activity against desmoid tumors, most likely because of c-*kit* and PDGFR RTK activity inhibition, and therefore warrants further study in the treatment of this challenging and difficult disease.

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